Researchers use ultrasound to safely, noninvasively induce a torpor-like state in mice and rats

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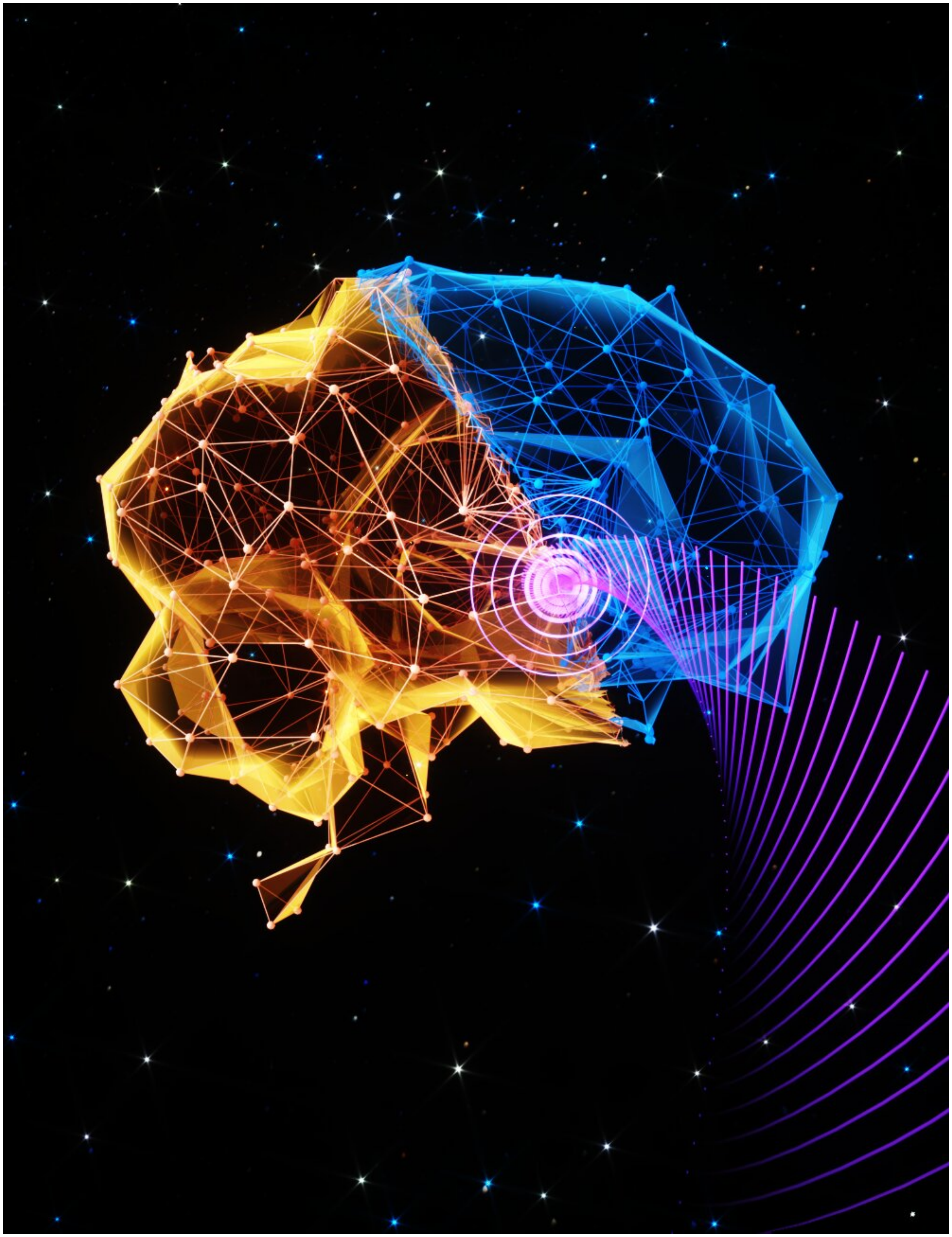

Hong Chen's team used ultrasound to safely, noninvasively induce a torpor-like state in mice, rats. Credit: Chen laboratory, Washington University in St. Louis

Some mammals and birds have a clever way to preserve energy and heat by going into torpor, during which their body temperature and metabolic rate drop to allow them to survive potentially fatal conditions in the environment, such as extreme cold or lack of food. While a similar condition was proposed for scientists making flights to space in the 1960s or for patients with life-threatening health conditions, safely inducing such a state remains elusive.

Hong Chen, an associate professor at Washington University in St. Louis, and a multidisciplinary team induced a torpor-like state in mice by using ultrasound to stimulate the hypothalamus preoptic area in the brain, which helps to regulate body temperature and metabolism. In addition to the mouse, which naturally goes into torpor, Chen and her team induced torpor in a rat, which does not. Their findings, published May 25, 2023, in *Nature Metabolism*, show the first noninvasive and safe method to induce a torpor-like state by targeting the central nervous system.

Chen, associate professor of biomedical engineering in the McKelvey School of Engineering and of radiation oncology at the School of Medicine, and her team, including Yaoheng (Mack) Yang, a postdoctoral research associate, created a wearable ultrasound transducer to stimulate the neurons in the hypothalamus preoptic area. When stimulated, the mice showed a drop in body temperature of about 3°C for about one hour. In addition, the mice's metabolism showed a change from using both carbohydrates and fat for energy to only fat, a key feature of torpor, and their heart rates fell by about 47%, all while at room temperature.

The team also found that as the acoustic pressure and duration of the ultrasound increased, so did the depth of the lower body temperature and slower metabolism, known as ultrasound-induced hypothermia and hypometabolism (UIH).

"We developed an automatic closed-loop feedback controller to achieve long-duration and stable ultrasound-induced hypothermia and hypometabolism by controlling of the ultrasound output," Chen said. "The closed-loop feedback controller set the desired body temperature to be lower than 34°C, which was previously reported as critical for natural torpor in mice. This feedback-controlled UIH kept the mouse body temperature at 32.95°C for about 24 hours and recovered to normal temperature after ultrasound was off."

To learn how ultrasound-induced hypothermia and hypometabolism is activated, the team studied the dynamics of the activity of neurons in the hypothalamus preoptic area in response to ultrasound. They observed a consistent increase in neuronal activity in response to each ultrasound pulse, which aligned with the changes in body temperature in the mice.

"These findings revealed that UIH was evoked by ultrasound activation of hypothalamus preoptic area neurons," Yang said. "Our finding that transcranial stimulation of the hypothalamus preoptic area was sufficient to induce UIH revealed the critical role of this area in orchestrating a torpor-like state in mice."

Chen and her team also wanted to find the molecule that allowed these neurons to activate with ultrasound. Through genetic sequencing, they found that ultrasound activated the TRPM2 ion channel in the hypothalamus preoptic area neurons. In a variety of experiments, they showed that TRPM2 is an ultrasound-sensitive ion channel and contributed to the induction of UIH.

In the rat, which does not naturally go into torpor or hibernation, the team delivered ultrasound to the hypothalamus preoptic area and found a decrease in skin temperature, particularly in the brown adipose tissue region, as well as about a 1°C drop in core body temperature, resembling natural torpor.

"UIH has the potential to address the long sought-after goal of achieving noninvasive and safe induction of the torpor-like state, which has been pursued by the scientific community at least since the 1960s," Chen said. "Ultrasound stimulation possesses a unique capability to noninvasively reach deep brain regions with high spatial and temporal precision in animal and human brains."

This multidisciplinary team consists of Jonathan R. Brestoff, MD, PhD, assistant professor of pathology and immunology at the School of Medicine; Alexxai V. Kravitz, associate professor of psychiatry, of anesthesiology and of neuroscience at the School of Medicine, and Jianmin Cui, professor of biomedical engineering in the McKelvey School of Engineering, all at Washington University in St. Louis. The team also includes Michael R. Bruchas, professor of anesthesiology and of pharmacology at the University of Washington.

More information: Hong Chen, Induction of a torpor-like hypothermic and hypometabolic state in rodents by ultrasound, *Nature Metabolism* (2023). DOI: 10.1038/s42255-023-00804-z. www.nature.com/articles/s42255-023-00804-z

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